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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/167,705	10/06/98	SCHMIDT	A 55873JPWJML

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EXAMINER	
HAMUD, F	
ART UNIT	**PAPER NUMBER**
1646	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

The copy

Office Action Summary	Application No. 09/167,705	Applicant(s) SCHMIDT et al
	Examiner Fozia Hamud	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Jan 12, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *10-69* is/are pending in the application.

Of the above, claim(s) *10-46, 53, and 69* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *47-52 and 54-68* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's submittal of the revised Sequence Listing and the computer readable form in Paper No.12 filed on 1/12/2000 is acknowledged. This Application now complies with the requirements of 37 C.F.R §1.824.

Election/Restriction

2. Applicant's election with traverse of Group IX in Paper No.7 filed on August 25,1999 is acknowledged. The traversal is on the ground that the inventions of Groups VIII, IX and X are all drawn to methods of inhibiting inflammation in a subject by administering a compound that is capable of interfering with the interaction between EN-RAGE peptide and RAGE , and that there would not be an undue burden on the Examiner to search these three groups together.

This traversal is found persuasive in part, even though, these three groups are all directed to methods of inhibiting inflammation, the agents or compounds used (anti-EN-RAGE antibodies, peptides or nucleic acid molecules), are patentably distinct and fall into different classes and subclasses, and a search of one will not necessarily reveal pertinent art on the others. However, the Examiner reconsidered the restriction and decided to examine Groups VIII and IX, (i.e the method of inhibiting inflammation in a subject by administering a peptide, and the method of inhibiting inflammation in a subject by administering anti-EN-RAGE antibodies) together. Group X will not be examined.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 10-46, 53 and 69 are withdrawn from consideration by the Examiner as they are drawn to non-elected inventions.

Thus Group VIII (claims 47-48, 50-52, 54-68) and Group IX (claims 47, 49-51, 54-68) are pending and under consideration by the Examiner.

Specification

3. A new title of the invention is required because, the word "novel" is not considered as part of the title of an invention, and the Patent and Trademark Office does not include such words at the beginning of the invention. It is suggested that the word "novel" be deleted from the title of the invention, See §M.P.E.P. 606.01.

Claim objections

4. Claim 54 are objected to because of the following informalities: Claim 54 is objected to because it is dependent on non-elected claim 26.

Claim Rejections - 35 U.S.C. § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 47-52 and 54-68, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting inflammation in a subject by administering soluble RAGE peptide (sRAGE), anti-RAGE or anti-EN-RAGE antibodies, does not reasonably provide enablement for a method of inhibiting inflammation in a subject by administering to said subject "all" possible compounds, or "all" possible peptides, or "all" possible antibodies and fragments thereof, that interfere with the interaction between EN-RAGE and its receptor. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 47 recites " a method for inhibiting inflammation in a subject which comprises administering to the subject a compound capable of interfering with the interaction between EN-RAGE peptide and RAGE ...", and claims 51 and 52 recite "...wherein the compound is a peptide, and wherein the peptide is an antibody or a fragment thereof...." respectively, while the specification discloses that in a mouse model of delayed hypersensitivity (DH), administration of sRAGE suppressed inflammation upon injection of methylated BSA (mBSA) into the foot pad of mice previously-sensitized with mBSA over the lymph nodes, in a dose-dependent manner,(see page 33, lines 28 through page 34 line 9, and figure 4) In the same model, the development of inflammation was also considerably suppressed with either anti-EN-RAGE $F(ab')_2$ or anti-RAGE $F(ab')_2$ and when mice were treated with both anti-EN-RAGE and anti-RAGE $F(ab')_2$, even further suppression of the inflammatory response was observed, (page 34, line 1 9 and figure 4). Figure 4 shows that sRAGE, anti-EN-RAGE $F(ab')_2$ or anti-RAGE $F(ab')_2$, all inhibit inflammation of the mouse model of delayed hypersensitivity, however, the instant specification does not illustrate whether this inhibition is because these agents interfere with the interaction between EN-RAGE and RAGE. In the mouse model of delayed hypersensitivity, inflammation is induced by injecting the mice with mBSA not by injecting the mouse with EN-RAGE, therefore, there is no correlation between inflammation and EN-RAGE. Instant specification fails to establish a nexus between the interaction of EN-RAGE with RAGE and inflammation. Since, RAGE is known to have other ligands, the possibility exists that sRAGE, and anti-RAGE $F(ab')_2$ interfere with the interaction between RAGE and "any" one of its

ligands, including EN-RAGE. The instant specification does not demonstrate that sRAGE, or anti-RAGE $F(ab')_2$ exclusively interfere with the interaction between EN-RAGE-RAGE, and by doing so inhibit inflammation. Thus the instant specification is only enabling for a method of inhibiting inflammation in a subject by administering anti-EN-RAGE antibodies, that interfere with the interaction between EN-RAGE-RAGE, and does not reasonably provide enablement for a method of inhibiting inflammation in a subject by administering to said subject "all" possible compounds, "all" possible peptides, or "all" possible antibodies, that may interfere with the interaction between RAGE and its receptor. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, in the instant application, the quantity of experimentation to determine which of the limitless possible compounds, peptides and antibodies, would interfere with the interaction between EN-RAGE and its receptor, is practically infinite and the guidance provided in the specification very little. The instant claims are not limited to naturally-occurring compounds and the instant specification does not provide examples of representative compounds that interfere with the interaction of EN-RAGE and its receptor. Anti-EN-RAGE and anti-EN-RGE $F(ab')_2$ fragment are the only peptides disclosed in the instant specification that interfere with the interaction between EN-RAGE and RAGE. Soluble RAGE and anti-RAGE antibodies would interfere with the interaction of RAGE and any of its ligands. Absent further

guidance from the specification it would constitute undue experimentation to determine all the other compounds that might interfere with the interaction between EN-RAGE and RAGE, as is encompassed by the scope of the claims. As such, claims 47-50-52 and 54 are not commensurate in scope with the specification but rather are broader than the supporting disclosure.

With respect to claims 55, 60, 67 and 68, which recite "....wherein the inflammation is associated with delayed hypersensitivity, accelerated atherosclerosis, lupus, septic shock, endotoxemia, autoimmune, bacterial-associated or other pathogen-associated infection", the instant specification is non-enabling for a method of treatment for any of the recited diseases, and is only enabling for a method of inhibiting inflammation associated with delayed hypersensitivity, (see page 33, lines 28 through page 34 line 9, and figure 4). The instant specification provides no disclosure that EN-RAGE/RAGE interaction is involved in accelerated atherosclerosis, lupus, septic shock, endotoxemia or bacterial-associated or other pathogen-associated infection, neither does it demonstrate that interfering with the interaction between EN-RAGE and RAGE would inhibit any of these diseases. Absent further guidance from the specification it would constitute undue experimentation to determine if all the recited diseases are induced by the interaction between EN-RAGE and RAGE, and if so, if blocking this interaction would inhibit these diseases. Therefore, the instant specification is only enabling for a method of inhibiting inflammation by administering anti-EN-RAGE antibodies or anti-EN-RGE $F(ab')_2$ fragment said anti-EN-RAGE antibodies interfering with the interaction between EN-RAGE and RAGE.

With respect to claim 64, the instant specification is non-enabling for a method of treatment, wherein the carrier comprises virus, or retro viral vector, there are no examples where either a virus

or a retro viral vector was used as a carrier for sRAGE, anti-RAGE or anti-EN-RAGE antibodies. Furthermore, it would be unpredictable if said vector or virus would make practical or safe carriers.

Claims 54, 56-59, 61-66 are rejected under 35 U.S.C. 112, first paragraph insofar as they depend on claim 47 for the limitations set forth directly above in this paragraph.

With respect to claim 47 which recites "a method for inhibiting inflammation in a subject which comprises administering to the subject a compound *capable* of interfering with the interaction between EN-RAGE and its receptor...." The specification is non-enabling for a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that does not interfere with the interaction between RAGE and its receptor, and is only capable of interfering if further modified, since Applicants have not taught how to further modify said compound such that it can interfere with the interaction between RAGE and its receptor. It has been held that an element is "capable of" performing a function is not a positive limitation but only requires the ability to perform. It does not constitute a limitation in any patentable sense. In re Hutchison, 69 USPQ 138. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 47-52, 54-68 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claims 47-48, 50, recite the acronym "EN-RAGE", and claims 49-50 recite the acronym "sRAGE", the recitation of these acronyms render these claims unclear and confusing. Applicants

are advised to recite the full names of the peptides in the first independent claim to obviate this rejection.

5b. Claim 50 recites "...wherein the compound *consists essentially* of the ligand binding domain of sRAGE or EN-RAGE....", however, it is unclear if the entire ligand binding domain of EN-RAGE or that of sRAGE is *essential* for the claimed compound or if only some parts of the domains are essential? What else should the claimed compound consist of? Clarification of this claim is required.

Claims 49, 51 and 54-68 are rejected as being vague and indefinite insofar as they depend on claim 47 for the limitations set forth directly above.

Claim rejections-35 U.S.C. § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6a. Claims 47-52, 56-59, 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hori et al (08/95), or Morser et al (US Patent 04/96) in view of Ritthaler et al (1995).

Hori et al disclose two ligands (a 12 kDa peptide and amphoterin), that bind to RAGE, and show that sRAGE and anti-RAGE $F(ab)_2$ antibodies block the interaction between RAGE and

amphoterin, (see abstract). Hori et al demonstrate that amphoterin binds RAGE with higher affinity than AGEs, they also show that RAGE has physiologically relevant ligands distinct from AGEs which are involved in physiologic processes other than diabetes and accumulations of AGE (abstract and page 25754, lines 1-6).

Morser et al teach a soluble human RAGE (sRAGE) and antibodies to RAGE that inhibit the ability of ligands (such as AGEs and amphoterin) to bind to RAGE, said sRAGE or antibodies being useful for disorders or symptoms which result from the association between RAGE and its ligands. (Column 6, lines 53-56 and column 11, lines 53-56). Morser et al also disclose methods of treatment for pathological disorders involving RAGE, by administering orally, intravenously, intra peritoneally or intramuscularly, an effective amount of sRAGE or anti-RAGE antibodies to a mammal, (column 19, lines 10-24 column 19, lines 56-60). However, neither Hori et al, nor Morser et al disclose a method of inhibiting inflammation by administering a compound that interferes with the interaction between RAGE and EN-RAGE.

Ritthaler et al disclose that the interaction of AGEs and RAGE may contribute to the development of vascular lesions and that examination of human atherosclerotic plaques or experimentally induced inflammatory lesions in response to local instillation of AGEs, showed prominent accumulation of cells strikingly positive for RAGE, (see abstract and page 688, column 2), thus implying that RAGE is involved in inflammation.

Therefore, it would have been prima facie obvious at the time of the invention to devise a method of inhibiting inflammation by administering the sRAGE or the anti-RAGE antibodies disclosed by Hori et al or Morser et al, because both Hori and Morser references demonstrate that

sRAGE and anti-RAGE antibodies block the interaction between RAGE and its ligands, and, Ritthaler et al teach that RAGE and its ligands are involved in inflammation. With respect to claims 58 and 59 which recite specific dosage of the claimed compound to be administered, and the schedule of administering said compound, respectively, it would have been obvious to one skill in the art to optimize the dosage and the schedule of administering the sRAGE and anti-RAGE antibodies taught by Hori or Morser, to get the most benefit for each patient. One of ordinary skill in the art would have been motivated to formulate a method of treatment for inflammation using the sRAGE or the anti-RAGE antibodies taught by Hori et al or Morser et al, because it is always desirous to develop a good therapy for inflammation and Ritthaler et al showed that RAGE and its ligands may play a role in inflammation..

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1646
March 20, 2000

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER